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10/049,887	09/20/2002	Yasunori Chiba	081356-0168	2894

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EXAMINER

PAK, YONG D

ART UNIT PAPER NUMBER

1652

DATE MAILED: 05/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/049,887

Applicant(s)

CHIBA ET AL.

Examiner

Yong D. Pak

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 April 2005.
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 88-105 is/are pending in the application.
4a) Of the above claim(s) 89-91 and 95-105 is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 88 and 92-94 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date see attached.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

This application is a 371 of PCT/JP00/05474.

The amendment filed on April 7, 2005, canceling claims 1-87 and adding claims 88-105, has been entered.

Claims 88-105 are pending. Claims 89-91, 95-99 and 100-101 are withdrawn. Claims 88 and 92-94 are under consideration.

Election/Restrictions

Applicant's election with traverse of Group III in the reply filed on April 7, 2005 is acknowledged. The traversal is on the ground(s) that there is unity of invention since all the claims are drawn to a method of producing glycoprotein by using a yeast comprising a disruption in the MNN1 gene, MNN4 gene and OCH1 gene, and these genes are a common technical feature to all the claims. This is not found persuasive because Chiba et al. (form PTO-1449) discloses such a mutant yeast. Therefore, the technical feature linking the above claims does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art. Also, claims 89-91, 95-99 and 100-101 and 103-105 are further drawn to yeast transformed with polynucleotides encoding proteins having different structure and function, which lacks the common technical feature with the method claimed in claims 88 and 92-94 and further requiring different searches in the patent and non-patent literature. Therefore, claims 88-105 do not all share a special technical feature.

The requirement is still deemed proper and is therefore made FINAL.

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Claims 89-91 and 95-105 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on April 7, 2005.

Newly submitted claim 100-105 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 100-101 are drawn to a method for producing a glycoprotein. Claims 102 -105 are drawn to mutant yeasts. However, Chiba et al. (form PTO-1449) discloses such a mutant yeast. Therefore, the technical feature linking the above claims does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

Furthermore, since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 100-102 and 105 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on February 4, 2005, August 5, 2004, July 16, 2003 and March 21, 2002 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Claim Objections

Claim 88 is objected to because of the following informalities: the claims recite the phrase "yeast mutant". It appears that applicants have meant to recite "mutant yeast". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 88 and claims 92-94 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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The terms "MNN1", "MNN4", "OCH1", "GnT-I", "ura3", "his3", "leu2", "ade2", "trp1" and "can1" are unclear. Reciting the full name of the genes and their function would overcome the rejection.

Claims 88 and 94 and claims 92-93 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 88 and 94 recite the term "gene". The metes and bounds of the term in the context of the above claims are not clear to the Examiner. A "gene" is generally understood in the art as comprising a coding sequence, introns, exons and regulatory sequences. A perusal of the specification did not provide the Examiner with a specific definition for the above term. Therefore, it is not clear whether the above term in said claims encompass the intronic and regulatory sequences or is limited to a cDNA. Examiner suggests replacing the above term with "polynucleotide".

Claim 88 and claims 92-94 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 88 recites the phrase "producing a glycoprotein". The metes and bounds of the phrase in the context of the above claim are not clear to the Examiner. It is not clear to the Examiner whether all glycoproteins produced in the mutant yeast cell will have the sugar chain of formula (IV) or only specific glycoproteins.

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Claim 94 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 94 recites the phrase "is derived from *Aspergillus saitoi*". The metes and bounds of this phrase are not clear to the Examiner. Literally, while the term "derived" means "to isolate from or obtain from a source", the above term could also mean "to arrive at by reasoning i.e., to deduce or infer" or also as "to produce or obtain from another substance". Therefore, it is not clear to the Examiner either from the specification or from the claims as to what applicants mean by the above phrase. It is not clear to the Examiner whether the mannosidase gene "derived from *Aspergillus saitoi*" encompasses a single specific gene as isolated from *Aspergillus saitoi*, or whether it encompasses recombinants, variants and mutants of the mannosidase gene or modified mannosidase gene from any other source and labeled as a mannosidase gene "derived from *Aspergillus saitoi*". As applicants have not provided a definition for the above phrase, Examiner has interpreted the claims broadly to mean that a mannosidase gene "derived from *Aspergillus saitoi*" encompasses polynucleotides which are recombinants, variants or mutants of any mannosidase gene. Examiner has given the same interpretation while considering the claims for all other rejections. The rejection can be overcome by amending the phrase to recite "wherein the polynucleotide encoding α -mannosidase I dehydrogenase is isolated from *Aspergillus saitoi*".

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 88 and 92-94 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 88 is drawn to a method of preparing a mutant yeast that produces the glycoprotein of formula (IV) by disrupting MNN1 gene, MNN4 gene and OCH1 gene in a wild-type yeast and transforming the resulting yeast with a polynucleotide encoding an α -mannosidase I and a polynucleotide encoding a GnT-I. Claims 92-93 limit claim 88 to specific auxotrophic mutations. Claim 94 is drawn to a method of preparing a mutant yeast that produces the glycoprotein of formula (IV) by disrupting MNN1 gene, MNN4 gene and OCH1 gene normally present in a wild-type yeast and transforming the resulting yeast with a polynucleotide encoding an *Aspergillus saitoi* α -mannosidase I and a polynucleotide encoding a GnT-I. These claims are drawn to a method of (A) mutagenizing any yeast to disrupt MNN1, MNN4 and OCH1 genes by any methods and (B) transforming said mutated yeast with a polynucleotide encoding any α -mannosidase I, including any recombinants, variants and mutants, and a polynucleotide encoding any GnT-I, including any recombinants, variants and mutants. Therefore, the claims are drawn to a method of mutagenizing any yeast that by disrupting a genus of MNN1, MNN4 and OCH1 genes and transforming said yeast with a polynucleotide encoding a

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genus of any α -mannosidase having any structure and a genus of GnT-I having any structure. There is insufficient descriptive support for using the above genus with respect to the yeast as well as α -mannosidase and GnT-I. The specification only teaches a method of preparing a *Saccharomyces cerevisiae* mutant by disrupting MNN1, MNN4 and OCH1 genes normally present in *S. cerevisiae* with selection markers recited in claim 92 and transforming the resulting *S. cerevisiae* mutant with a polynucleotide encoding α -mannosidase I and a polynucleotide encoding a rat GnT-I (cloned by Yoshida et al – form PTO-1449) isolated from *A. saitoi*. This one example is not enough and does not constitute a representative number of all the species to describe a method of mutagenizing any or all yeast using any method and transforming the resulting yeast with a polynucleotide encoding any or all α -mannosidase I and GnT-I, including any or all mutants, variants and recombinants. Further, there is no evidence on the record of the relationship between the structure of any or all yeast and the structure of a polynucleotide encoding an *A. saitoi* α -mannosidase I and the structure of any or all recombinants, variants and mutants of a polynucleotide encoding any α -mannosidase I or the structure of a polynucleotide encoding a rat GnT-I and the structure of a polynucleotide encoding any or all recombinants, variant or mutants of any GnT-I. Therefore, the specification fails to describe a representative species of mutagenizing a genus of yeast by disrupting a genus of MNN1, MNN4 and OCH1 genes by any methods and transforming the resulting yeast with a polynucleotide encoding a genus of α -mannosidase I and a genus of GnT-I.

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Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 88 and 92-94.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov <<http://www.uspto.gov>>.

Claims 88 and 92-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of preparing a mutant *Saccharomyces cerevisiae* by disrupting MNN1, MNN4 and OCH1 genes normally present in *S. cerevisiae* with selection markers recited in claim 92 and transforming the resulting mutant *S. cerevisiae* with a polynucleotide isolated from *Aspergillus saitoi* and encoding an α -mannosidase I and a polynucleotide isolated from rat and encoding a rat GnT-I, does not reasonably provide enablement for a method of preparing any mutant yeast that produces the glycoprotein of formula (IV) by disrupting any or all MNN1, MNN4 and OCH1 genes and transforming the resulting mutant yeast with a polynucleotide encoding any α -mannosidase I, including recombinants, variants and mutants, and a polynucleotide encoding any GnT-I, including recombinants, variants and mutants. The specification does not enable any person skilled in the art to which it

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pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claim 88 is drawn to a method of preparing a mutant yeast that produces the glycoprotein of formula (IV) by disrupting MNN1 gene, MNN4 gene and OCH1 gene in a wild-type yeast and transforming the resulting yeast with a polynucleotide encoding an α -mannosidase I and a polynucleotide encoding a GnT-I. Claims 92-93 limit claim 88 to specific auxotrophic mutations. Claim 94 is drawn to a method of preparing a mutant yeast that produces the glycoprotein of formula (IV) by disrupting MNN1 gene, MNN4 gene and OCH1 gene normally present in a wild-type yeast and transforming the resulting yeast with a polynucleotide encoding an *Aspergillus saitoi* α -mannosidase I and a polynucleotide encoding a GnT-I. These claims are drawn to a method of (A) mutagenizing any yeast, (B) disrupting MNN1, MNN4 and OCH1 genes by any methods and (C) transforming said mutant yeast with a polynucleotide encoding any α -mannosidase I, including any recombinants, variants and mutants, and a polynucleotide encoding any GnT-I, including any recombinants, variants and mutants. Therefore, the

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claims are drawn to a method of mutagenizing any yeast by disrupting MNN1, MNN4 and OCH1 genes having any structure in any yeast using any methods and transforming said yeast with a polynucleotide encoding any α -mannosidase having any structure I and any GnT-I having any structure. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of yeasts using any methods for transforming the resulting yeast with polynucleotides encoding any or all variants, mutants and recombinants of any α -mannosidase I and any GnT-I broadly encompassed in the method of the claims. Since applicants have not shown that the claimed method applies to all or any yeast and since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which specific yeast is ideal for the claimed method and in the case of polynucleotides encoding mannosidase and GnT-I, used to transform said mutated yeast, which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The claims also encompass a method of introducing double bonds into any position within a steroid skeleton using any bacterial host cell.

However, in this case the disclosure is limited to a method of preparing a *Saccharomyces cerevisiae* mutant by disrupting MNN1, MNN4 and OCH1 genes normally present in *S. cerevisiae* with selection markers recited in claim 92 and

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transforming the resulting *S. cerevisiae* mutant with a specific polynucleotide isolated from *Aspergillus saitoi* encoding α -mannosidase I and a polynucleotide isolated from rat encoding GnT-I (cloned by Yoshida et al – form PTO-1449), but provides no guidance with regard to a method of comprising the use of any yeast for disrupting any or all MNN1, MNN4 and OCH1 genes using any methods and transforming the resulting mutant yeast with a polynucleotide encoding any α -mannosidase I and a polynucleotide encoding any GnT-I. It would require undue experimentation of the skilled artisan to make and use the agents in the claimed method. In view of the great breadth of the claim, amount of experimentation required to mutagenize any yeast, identify and make the polynucleotides encoding any α -mannosidase I and GnT-I, amount of experimentation required to disrupt any MNN1, MNN4 and OCH1 genes using any methods, the lack of guidance, working examples, and/or unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polynucleotides and yeasts encompassed by the claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques and other related techniques are known, and it is routine in the art to screen for multiple strains, multiple substitutions or multiple modifications in a polypeptide as encompassed by the instant claims, the specific yeast strains required for the method and the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility for

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transforming said mutant yeast are limited in any protein and the result of such modifications is unpredictable. In addition, with respect to the polynucleotides encoding mannosidase and GnT-I used for transforming mutant yeast, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass a method of preparing any yeast by disrupting any or all MNN1, MNN4 and OCH1 genes using any methods and transforming the resulting mutant yeast with a polynucleotide encoding any α -mannosidase I and a polynucleotide encoding any GnT-I because the specification does not establish: (A) said method will be successful in any or all yeasts; (B) a universal method disrupt any MNN1, MNN4 and OCH1 genes in any yeast; (C) a rational and predictable scheme for selecting agents, techniques or methods with an expectation of disrupting any MNN1, MNN4 and OCH1 genes in any yeast; (D) the general tolerance of α -mannosidase I and GnT-I to modification and extent of such tolerance; (E) a rational and predictable scheme for selecting any yeast for disrupting MNN1, MNN4 and OCH1 genes and transforming the resulting yeast with a polynucleotide encoding any α -mannosidase I and GnT-I with an expectation of making a mutant yeast that produces the glycoprotein of formula (IV); and (F) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated

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with the scope of the claims broadly including a method of preparing any mutant yeast by disrupting any or all MNN1, MNN4 and OCH1 genes using any methods and transforming the resulting mutant yeast with a polynucleotide encoding any α -mannosidase I and a polynucleotide encoding any GnT. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of yeasts suitable for the above method and polynucleotides encoding an α -mannosidase I and GnT- having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 88 and 92-94 rejected under 35 U.S.C. 102(b) as being anticipated by Chiba et al.

Claims 88 and 92-94 are drawn to a method of preparing a mutant yeast that produces the glycoprotein of formula (IV) by disrupting a MNN1, MNN4 and OCH1 genes using the selection markers recited in claim 92 and introducing a polynucleotide

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encoding α -mannosidase I, such as that of *A. saitoi*, and a polynucleotide encoding GnT-I into the resulting mutant yeast.

Chiba et al. (form PTO-1449) discloses a method of preparing a mutant yeast that produces the glycoprotein of formula (IV) by transforming a *S. cerevisiae* comprising $\Delta mnn1\Delta mnn4\Delta och1$ triple mutant with a polynucleotide encoding an *A. saitoi* α -mannosidase I and a polynucleotide encoding GnT-I into (Figure 1 and pages 26299-26300). The *S. cerevisiae* $\Delta mnn1\Delta mnn4\Delta och1$ mutant was prepared by disrupting the MNN1, MNN4 and OCH1 genes with selection markers as recited in claim 92. Therefore, the reference of Chiba et al. anticipates claims 88 and 92-94.

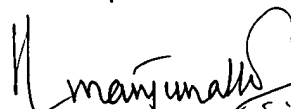
None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are ~~571-273-8300 for regular communications and 703-872-9307 for After Final communications.~~

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner 1652


Manjunath Rao
Primary Examiner 1652